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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/597,286	10/20/2006	Jose Vicente Castell Ripoll	020884-000009	8850

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EXAMINER	
QIAN, CELINE X	

ART UNIT	PAPER NUMBER
1636	

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03/15/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/597,286	RIPOLL ET AL.	
	Examiner	Art Unit	
	CELINE X. QIAN	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 December 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9,11 and 13-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,11 and 13-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 July 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-9, 11, 13-19 are pending in the application.

This Office Action is in response to the Amendment filed on 12/1/09.

Response to Amendment

The objection to claims 2-8 and 14-20 has been withdrawn in light of the amendment to the claims.

The rejection of claims 1-8 and 13 under 35 U.S.C. 112 2nd paragraph has been withdrawn in light of amendment to the claims.

The rejection of claim 13 under 35 U.S.C. 102 (b) has been withdrawn in light of the amendment to the claim.

The rejection of claims 1-9, 11, 13-20 under 35 U.S.C. 103 (a) is maintained for reason set forth of the record mailed on 9/1/09 and further discussed below.

Response to Arguments

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-9, 11, 13-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bort et al (IDS), in view of Gomez-Lechon et al (IDS).

Gomez-Lechon et al. teach that *in vitro* metabolism models can speed up the identification of new drug candidates, and pharmaceutical companies are increasingly making use of such model. Gomez-Lechon et al. discuss advantages and limitation of currently existing *in vitro* models including liver microsomes, human heptocytes and CYP engineered cells (see Table 1). Gomez-Lechon et al. teach that using human hepatocytes for this application has limitations such as losing expression of many hepatic proteins including CYPs during culture (see page 297, 1st col., 2nd paragraph). Gomez-Lechon et al. also teach that using hepatic cell lines expressing single CYP has limitations including lack of phase II enzymes, uncoupled metabolic pathways, no physiological levels of enzymes, impossibility of induction studies and no in *vitro/in vivo* correlations (see Table 1). Moreover, in cDNA-expressing systems a single CYP interacts with an electron-carrier/supplier protein, while in liver hepatocytes many CYPs can interact with them, thus lead to incorrect predictions of the relative distributions of individual CYPs to the metabolism of a drug (see page 299, 1st col., last paragraph). Gomez-Lechon et al. further indicate that the future improvements for those CYP engineered cells to serve as *in vitro* model includes co-expression of several CYPs, expression of phase II enzymes and development of cells responsive to induction (see Table I). Gomez-Lechon et al. state that there is a need for

hepatic cell lines expressing the whole spectrum of human xenobiotic-metabolizing enzymes as an alternative to primary cultures, and the hepatic-specific expression of a given gene is accomplished by the concerted action of a number of liver-enriched and ubiquitous regulatory factors. Gomez-Lechon et al. suggest that a promising experimental approach is the use of adenoviral vectors to allow simultaneous expression of multiple genes (see page 307, bridging paragraph). Gomez-Lechon et al. teach that adenoviruses encoding two of the most relevant liver enriched transcription vectors have been successfully generated and transduced to HepG2, a cell line of hepatic origin.

However, Gomez-Lechon et al. do not teach actual practice of the suggested approach of transfecting multiple adenoviral vector that expresses different phase I or phase II enzyme to cells of hepatic origin.

Bort et al. teach a method of studying hepatic metabolism of diclofenac using liver epithelial cell lines that transfected with specific CYP genes (see page 792, last paragraph through page 793, 1st col.). Bort et al. teach that comparison of metabolism of diclofenac in both primary hepatocytes and said genetically engineered cell lines is able to identify CYP that are required for said drug metabolism (see page 793, last paragraph and Figure 7).

It would have been obvious an ordinary skill in the art to introduce adenoviral expression vectors that expresses different Phase I or Phase II enzymes to cells of hepatic origin to build an *in vitro* model for studying drug metabolism based on the teaching of Gomez-Lechon et al. The teaching of Gomez-Lechon et al. clearly established that there is a need for such engineered cell line to be made for the purpose of studying drug metabolism. Bort et al. has demonstrated that this approach is feasible using hepatic cell lines transfected vector expressing single CYP

enzymes and assessing hepatic metabolism of diclofenac. Since Gomez-Lechon et al. taught the limitation of cell line expressing single CYP, an ordinary skilled in the art would have been motivated to modify such system by introducing additional Phase I or Phase II enzymes such that the cell line will reflect the whole spectrum of human xenobiotic metabolizing enzyme expression profile. The level of skill in the art is high as evidenced by transducing hepatic cell lines using adenoviral vectors have been proven successful, and the identification of cDNA encoding Phase I and Phase II enzymes wherein such information is available to the public. The ordinary artisan having the knowledge of cDNA encoding of Phase I and Phase II enzymes would have reasonable expectation of success to generate adenoviral vectors expressing sense or anti-sense drug metabolizing enzymes to up or down-regulating specific enzymes in a cell of hepatic origin to best mimic the hepatocytes *in vivo*. Once such *in vitro* model is made, it would have been obvious to the ordinary artisan to use such model to study metabolism, pharmacokinetics, potential idiosyncratic heptotoxicity and or potential medicament interaction of a drug as claimed. The claimed cells expressing different phase I or phase II enzymes and the method of making them by transfecting cells with adenoviral expression vectors would have been obvious because a person of ordinary skill in the art has good reason to pursue the known options within his or her technical grasp, in the instant case, as suggested by Gomez-Lechnon et al., to make the claimed cell model. As stated above, the ordinary artisan having the knowledge of cDNA encoding of Phase I and Phase II enzymes would have reasonable expectation of success to generate adenoviral vectors expressing sense or anti-sense drug metabolizing enzymes to up or down-regulating specific enzymes in a cell of hepatic origin. Therefore, the claimed

invention is not of innovation but of ordinary skill and common sense, and would have been *prima facie* obvious to the ordinary artisan at the time the invention was made.

In response to this rejection, Applicants argue that Gomez-Lechon's suggestion of using multiple adenviral vectors to express multiple genes is made only in the context of regulating the expression of transgenes, but not expressing Phase I and II enzymes simultaneously in hepatic cells. Applicants argue that Gomez-Lechon does not provide a motivation to express enzymes of Phase I and II using a set of more than one recombinant adenoviral expression vectors. Applicants further assert that the claimed method allows for the regulation of the expression levels of the enzyme since there is a correlation between the dosage of adenoviral particles and the expression level of the enzyme encoded by the corresponding adenovirus. Applicants further argue that Bort does not mention the possibility of using a set of more than one recombinant adenoviral vectors, or of coding for a different phase I or II biotransformation enzyme as claimed in the application. Applicants assert that in combination, the contents of Bort would not have prompt one of ordinary skill in the art to modify the cell model disclosed in Gomez-Lechon so as to incorporate additional phase I or II biotransformation enzymes, let alone to incorporate additional enzymes by use of adenoviral vectors when attempting to achieve a controlled expression of the metabolic enzymes. Lastly, Applicants argue that the process of achieving a need for engineered cell line for the purpose of studying drug metabolism is not obvious because the process is unknown.

The above arguments have been fully considered but deemed unpersuasive. The detailed reason for obviousness of the claimed invention was discussed in the previous office action and above. In response to applicant's arguments against the references individually for lack of

teaching of introducing multiple adenoviral vectors encoding different CYP enzymes to a hepatic cell, Applicants are reminded that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Moreover, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). The examiner also recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). As set forth in the rejection, upon reading the Gomez-Lechon reference, the ordinary artisan would have realized the advantage of using hepatic cells to study drug metabolism and the limitation of using cells transfected with single CYP enzyme, it would have been obvious to the ordinary artisan to try to introduce additional Phase I or Phase II enzymes such that the cell line will reflect the whole spectrum of human xenobiotic metabolizing enzyme expression profile. The concept of introducing multiple CYP enzymes into hepatic cell while it is clear that single CYP expression has limitation for the intended purpose would have been obvious because it is within the technical grasp of an ordinary artisan to pursue known options. Contrary to Applicant's

assertion, the advantage of expressing multiple genes using adenoviral vectors has been taught in Gomez-Lechon (see page 307, 2nd col., 1st paragraph). Even if this suggestion is made only in the context of regulating the expression of CYP isoforms by modulating the activity of a family of transcription factors known as liver-enriched and ubiquitous regulatory factors specific for each of said CYP isoforms as alleged by Applicants, the ordinary artisan reading this section would have realized that such transcription factors are responsible for the expression of a number of isoforms of CYP and can induce their expression in a controlled manner. Since the purpose is to induce expression of multiple CYP in hepatic cells, expressing ectopic CYP would have the same effect, which is an obvious alternative to expressing the transcription factor. To pursue a known option is within the capability of an ordinary skill of art. If it leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. Therefore, for reasons discussed in the previous office action and above, this rejection is maintained.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CELINE X. QIAN whose telephone number is (571)272-0777. The examiner can normally be reached on 10-6:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Celine X Qian /
Primary Examiner, Art Unit 1636